Title:

Assessment of a Tailored Home-Based Exercise Program on Symptoms, Well-Being, and Resilience among Cancer Survivors with multiple chronic conditions

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Study Protocol and Analysis Plan
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JHM IRB - eForm A – Protocol

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1. Abstract

The benefits of physical activity on managing chronic illnesses and multiple symptoms are well established. However, increasing the physical activity of persons living with Multiple Chronic Conditions (MCC), especially low –income cancer survivors with MCC, is challenging. Home-based exercise improves physical activity and symptoms among persons with the single chronic disease. One major challenge of the home-based exercise is the motivation and adherence. The mobile technologies (e.g., wearable device and smartphone application) have been used to improve motivation and monitor a person physical activity. Guided by the society to cells framework and previous preliminary findings, we developed a technology-enhanced home-based exercise program using a combination of the integrated mobile technologies (wearable device and phone application) and tailored home-based exercise. Participants will choose one of the four home-based exercise options (National Institute of Aging [NIA] Go4Life, Iyengar-style yoga, walking, and modified Otago exercise) based on their preference and goals. The integrated mobile technologies system will allow us to extract heart rate data directly from the wearable device to the research server. This data will be used to provide appropriate and personalized feedback on physical performance and trigger algorithms to send the survey and notification to the participants in real time. This pilot project will examine the feasibility of this technology-enhanced home exercise tailored to participants' goals and preferences. The intervention will leverage the cancer survivorship phase (post-treatment) to motivate self-care by combining tailored existing evidence-based physical activity programs and mobile technology for participants to engage in the resilience-enhancing physical activity. Identification of BDNF's role as one of the exercise outcomes provide a novel target for an intervention and increase our understanding of the underlying mechanism of symptoms and resilience.

2. Objectives (include all primary and secondary objectives)

This study consists of 2 phases.

Phase 1:

Aim 1: Examine the feasibility and acceptability of the iBHE program among low-income cancer survivors living with co-morbid conditions. Eight participants who have completed treatment for a solid tumor cancer with at least one comorbidity (e.g., diabetes and/or hypertension) will be assigned to an open-label trial of the idea. We will gather feedback on goal setting, problem-solving strategies, exercise choices, and tracking mechanisms, program feasibility, and acceptability and modify the intervention as needed prior to Phase 2.

Phase 2:

Aim 2: pilot testing the effect of the tailored iHBE on fatigue, pain, affective well-being, resilience and BDNF level among low-income cancer survivors living with co-morbid

conditions at completion (12 weeks) and 6 months in comparison to usual care waiting list group. After adjustment in the protocol based on Aim 1, 50 participants who meet the inclusion criteria will be randomly assigned to a 12-week experimental (preferred physical activities) group or a usual care usual care (waiting list) group. Variables will be measured at baseline, completion (12 weeks) and 6 months. *Hypothesis 2: After controlling for the age, gender, race, and BMI, participants in the experimental group will have a great decline in fatigue, pain, and a greater increase in AWB, resilience and BDNF level from baseline to program completion and 3 months compared to the usual care group.*

Aim 3: Examine the association between the changes in the biomarker (BDNF) in serum and sweat after the 12-weeks from baseline and at 3 months post program completion from baseline iBHE program. *Hypothesis 3: the change in the serum BDNF level is positively associated with a change in the sweat BDNF level at the after the 12-weeks from baseline and at 6 months from baseline iBHE program.*

The purpose of this phase 1 pilot study is to examine the feasibility, acceptability and preliminary efficacy of a promising home-based, tailored, technology-enhanced exercise program (iHBE). The intervention is guided by the *Society to Cells* framework and tailors activity based on the individual's preferences, resources, and readiness and it harnesses technology to provide a reminder and immediate feedback on physical performance.(Blaney, Lowe-Strong, Rankin-Watt, Campbell, & Gracey, 2013; Studenski et al., 2010) After pilot testing the feasibility and acceptability of the intervention, we will conduct an RCT to examine the preliminary efficacy of the item on health outcomes (fatigue, pain, AWB, resilience, and BDNF) among low-income cancer survivors living with MCC. We will obtain measures at baseline and 4-week follow-up using a combination of self-report and objective measures. Brain-derived neurotrophic factor (BDNF) is a protein in oxidative stress pathway(Markham et al., 2012) that is related to fatigue(Saligan, Lukkahatai, Holder, Walitt, & Machado-Vieira, 2015) and resilience.(Holmes, 2014) A consistent, light-intensity aerobic exercise can significantly increase 25% of serum BDNF level from baseline.(Zimmer et al., 2017) We propose to examine this biomarker as one of the outcomes to identify the potential biological mechanism of pain, fatigue, and resilience. BDNF testing does not account for circadian rhythm nor temporality to exercise and requires venipuncture. Therefore, a secondary goal of this study is to examine the level of sweat BDNF, non-invasively collected over 72 hours in comparison to serum BDNF. The specific aims of this phase 1 pilot project are to **examine the feasibility and acceptability of the iBHE program among low-income cancer survivors living with co-morbid conditions.** Eight participants who have completed treatment for a solid tumor cancer with at least one comorbidity (e.g., diabetes and/or hypertension) will be assigned to an open-label trial of the iBHE. The feasibility of this first study phase is defined as the acceptability, compliance, and delivery of the intervention. The feasibility of the intervention program will be determined from the achievement of individual physical activity goal. At the end of 4 week program, research team will review the participants ability to achieve at least 75% of the individual's exercise goal (for example, if the goal is to exercise at the fat burn level (50-60% maximum heart rate measured by FitBit) for 30 min/day 3 days week, participants can exercise for 30 min for at least 2 days or FitBit data showed more than 60 active min). For this first phase, at least 50% of participants will need to meet 75% of personal goal in at least 2 weeks for the trial to continue onto phase II. For participants who do not achieve 75% of their individual exercise goal, the barriers will be identified that the weekly goals will be revised until the 75% of weekly personal exercise goals is met. If the feasibility threshold (less than 50% of participants achieve 75% of their weekly goals for 2 weeks) does not reach, we will adjust the goal setting process and recruit more participants. We will conduct a qualitative semi-structured interviews interview to gather feedback on goal setting, problem-solving strategies, exercise choices, and tracking mechanisms, program feasibility, and acceptability and modify the intervention as needed. The descriptive information in this phase I to help inform alternative

approaches to the anticipated analysis, sample size estimates for phase II, and additional key variables to be measured in phase II (intervention dose, fidelity, and .additional process variables).

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Nearly 16 million Americans were cancer survivors in 2016, with an additional 1.7 million new cases expected in 2017.(American Cancer Society, 2017) With the advancement of cancer diagnosis and treatment, 60% of cancer patients will survive at least 5-years.(National Cancer Institute, 2014) More than 80% of these cancer survivors have one or more comorbid chronic conditions (e.g., type 2 diabetes, cardiovascular diseases, osteoarthritis)(Rothrock et al., 2010) with hypertension as a most frequent comorbid condition (prevalence rate of 20-65%).(Braithwaite et al., 2009; Izano et al., 2014; Shin et al., 2008) This prevalence of these MCCs is double (60-75%) among older adults and even higher among low income older adults.(Kramarow, 2017) This growing MCCs prevalence affects health status, disability and AWB.(Koolhaas et al., 2013) Studies show that the number of MCCs is associated with the prevalence and severity of symptoms such as pain and fatigue.(Annunziata, Muzzatti, Mella, & Bidoli, 2013; Arrieta et al., 2013; Manning & Bettencourt, 2011; Servaes, Gielissen, Verhagen, & Bleijenberg, 2007) These multiple symptoms impact persons' AWB and adherence to the treatment.(Beck, Towsley, Caserta, Lindau, & Dudley, 2009; Shelby et al., 2011) Persons living with MCCs with multiple symptoms have a greater risk of premature death than those without symptoms.(Cheville et al., 2011; Yang et al., 2012) Cancer survivors with multiple chronic conditions experience significantly higher symptoms such as pain, and fatigue prevalence and severity than those without comorbidity.(Annunziata et al., 2013; Arrieta et al., 2013; Huang, Hudson, Robison, & Krull, 2017; Manning & Bettencourt, 2011; Servaes et al., 2007) Managing these multiple chronic conditions and multiple symptoms requires active participation from the persons and family members. ***Socioeconomic status (SES) complicates the management of these multiple conditions, as people with low income can have limited access to health care and resources, limited leisure-time, and other non-medical challenges.(Beenackers et al., 2012)***

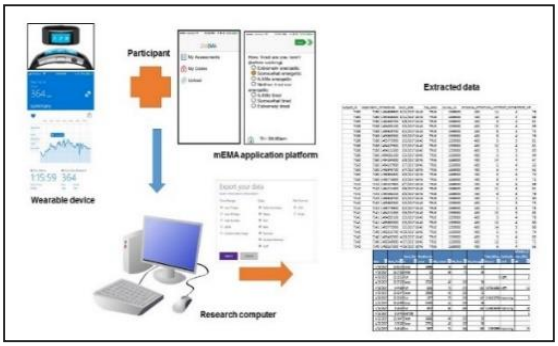
The US Centers for Disease Control and Prevention recommends increasing physical activity (PA) as one of the most effective interventions for managing chronic conditions and symptoms.(National Comprehensive Cancer Network (NCCN), 2017) Exercise is a type of PA that required structure, repetition of an intentional movement. ***Studies show a continuous aerobic moderate-intensity exercise program not only improves fatigue, pain,(Dodd et al., 2010; Meneses-Echavez, Gonzalez-Jimenez, & Ramirez-Velez, 2015a, 2015b; Tian, Lu, Lin, & Hu, 2015; van Waart et al., 2015) and AWB,(Cheville et al., 2010) but also delays the onset and progression of other chronic conditions.*** In spite of the benefit of PA, evidence shows that less than 10% of cancer survivors are active during treatment and only 20% of cancer survivors are active after treatment.(Pinto & Ciccolo, 2011) The number is even lower in low-income cancer survivors with comorbidities. To overcome barriers to exercise, home-based exercise programs have been developed and report promising effectiveness on pain, fatigue, and AWB among persons with several chronic conditions.(Dodd et al., 2010; Hoffman et al., 2013; Spector, Deal, Amos, Yang, & Battaglini, 2014) However, these studies examined the effectiveness of these program on an individual chronic condition. They reported that most home-based exercise programs are challenged by a lack of motivation and low engagement rate with the exercise regimen.(Junghaenel, Cohen, Schneider, Neerukonda, & Broderick, 2015; Kober et al., 2015; Wright et al., 2015a, 2015b) Recent evidence shows that the use of technology to provide immediate feedback on physical performance and reminder messaging can increase motivation and adherence to PA.(Blaney et al., 2013; Studenski et al., 2010) This is part of the scientific premise for this study.

Resilience is defined as a positive adaptation and maintenance function during stressful events.(Eicher, Matzka, Dubey, & White, 2015) It influences the perception of symptoms including pain and fatigue.(Kennedy et al., 2017; Lim, Shon, Paek, & Daly, 2014; Sharpley et al., 2017; Sharpley, Bitsika,

Wootten, & Christie, 2014; Strauss et al., 2007; Szanton & Gill, 2010) People with high resilience report lower pain, fatigue and better physical functioning and AWB than those with low resilience.(Deshields, Heiland, Kracen, & Dua, 2016; Eicher et al., 2015; Hou & Lam, 2014; Matzka et al., 2016) The PA intervention can improve resilience by triggering an adaptive mechanism for neurodegeneration.(Pedrinolla, Schena, & Venturelli, 2017) Stress suppresses neurogenesis in the hippocampal area of the brain through BDNF.(Malberg, 2004; Malberg & Schechter, 2005) BDNF is a member of the neurotrophic family of proteins that plays a significant role in neuronal survival.(Markham et al., 2012) BDNF can be modulated by oxidative stress during physical and psychological stressful events (e.g., inflammation, extreme exhaustion). During stressful events, BDNF is activated to enhance neuroprotective mechanisms.(Scuri, Samsell, & Piedimonte, 2010) BDNF has been proposed to influence resilience.(Holmes, 2014; Rothman & Mattson, 2013; Tyagi, Zhuang, Agrawal, Ying, & Gomez-Pinilla, 2015) Exercise can affect the BDNF level. A study in cancer survivors reported that 8 months of a personalized light-intensity aerobic exercise (15-25 MET h/week) can significantly increase 25% of serum BDNF level from baseline. (Zimmer et al., 2017) Based on the meta-analysis the 12 week is the duration for exercise program most studies used to see the change in BDNF level.(Dinoff et al., 2016)

Framework: The iBHE program is based on the Society to Cells Resilience framework and promising findings from two previous studies. The intervention targets two domains; individual and physiological factors (neurochemical activities). The intervention aims to promote individual's ability in reflection, affirmation, goal setting, dealing with ambivalence and change in stress-induced neurochemical activity through tailoring and physical performance feedback through mobile technologies, which will improve resilience, pain, fatigue, AWB and BDNF level.

Preliminary works: The scientific premise of the proposed study is based on the findings from two preliminary studies.



Study 1: We tested the feasibility of a home-based exercise program that integrated a PA tracking device and an ecological momentary assessment mobile phone application (mEMA) to enhance and track home-based exercise in one week among 30 healthy volunteers. We asked the participants to walk or run at least 30 min to increase HR to at least 60% of maximum possible HR for 5 days while wearing the wearable device and response to the survey on the smartphone application. ***Our preliminary results showed that the integrated system is feasible and easy to use. We were able to monitor exercise adherence through the heart rate monitoring. Participants preferred the information about steps, heart rate, and calorie during the PA provided by the wearable device.*** However, our preliminary study did not have a focus on low-income people with MCC who have additional challenges in engaging in the recommended amount of exercise. In addition, our previous work did not tailor the exercise to the context or preference of participants which can be ***improved by assessing persons' readiness and intention, and tailoring the program to individual needs.***(Husebo, Dyrstad, Soreide, & Bru, 2013; Puts et al., 2014)

Study 2: Our recent publication reported the association between BDNF and fatigue. **We found that cancer survivors with worsening fatigue during radiotherapy had significant lower BDNF level than the non-fatigue survivors.**(Saligan et al., 2015)

This study, we will examine an integration of tailored home exercise and mobile technologies to improve resilience, pain, fatigue, and AWB among low-income cancer survivors with MCC. To address the limitations of engagement to exercise intervention, we will combine our previous smartphone application and wearable technology with goal setting and problem-solving intervention to tailor PA to individual daily

life and physical fitness goals, and preference. Participants' steps count and heart rate will be continuously monitored by the wearable device to measure adherence and intensity of the PA at home.

4. Study Procedures

This study will be conducted in two phases.

Phase one (Aim 1) is the intervention trial phase (open-label phase):

Design: Mixed methods design.

The aim of this phase (specific aim 1) is to obtain participants' perception and acceptability of the program. The number of eligible participants and recruited participants, the number of participants completing the intervention program, and the number of drop out participants will be recorded. The program will be adjusted based on the participant feedback and will be pilot tested in phase 2. *We are submitting this application for phase one at this time and will submit phase 2 in the further study action.*

Sample and Setting:

The study participants will be recruited from the home health care agencies in Baltimore, Maryland, Johns Hopkins Comprehensive Cancer Center and Johns Hopkins Hospital.

Inclusion criteria are (1) participants diagnosed with solid tumor cancer who have completed cancer treatment at least 6 months; (2) diagnosed with diabetes and/or hypertension for at least a year; (3) aged 21 years or older, (4) have an annual household incomes of below $30,000 for families of three, (5) the average fatigue level within the past 7 days at the level of 3 or more on the 0 (no fatigue) to 10 (worse fatigue) Likert scale and (6) give informed consent.

Exclusion criteria are those (1) currently undergoing treatment for cancer; (2) have an active infection (e.g., fever, localized redness, swelling, sinus congestion); and/or (3) diagnosed with a psychological disorder (e.g., suicidal or homicidal tendencies, extreme anxiety or depression).

Data Collection Schedule and Procedures. Upon receiving approval from the Johns Hopkins University Institutional Review Board, the study flyer will be posted and distributed at the home health care agencies in Baltimore, Maryland, Johns Hopkins Comprehensive Cancer Center and Johns Hopkins Hospital.

Recruitment, Informed Consent, and Confidentiality. Recruitment methods for this study include (1) distributing and posting flyers, with a tear-off phone number to speak with the principal investigator (PI) as necessary, posted at the hospital (2) face-to-face recruitment for potential participants during cancer support group meetings; and (3) word-of-mouth. Potential participants will receive a verbal explanation by phone or face to face meeting in terms suited to their comprehension of the purpose, procedures, and potential risks of the study. During the screening for eligibility process, an oncologist will be available for consultation. The oncologist will be notified and consulted for the appropriateness of the exercise for participants who self-report having co-morbidities. The participants and family or legal guardian will have an opportunity to carefully review the consent form and ask questions regarding this study prior to signing. Participants will be encouraged to consult with their primary doctor if any concern or an additional question. Participants will be informed that they may withdraw from the study at any time without prejudice to themselves.

Participants will be approached and screened for the annual income below $30,000 for families of three, average fatigue level within the past 7 days at the level of 3 or more on the 0 (no fatigue) to 10 (worse fatigue) Likert scale, the self-report perceived ability to walk for six-minute and the exertion level after the walk on a 0-10 numeric perceived exertion scale (0 = no exertion at all to 10 = maximal exertion). Eligible participants will be asked if they would like to participate and to sign the informed consent. Participants

will be asked to have the research team visit their home for the initial assessment and to provide instruction on the exercise, the physical activity tracker and how to complete the questionnaire via the phone application. Participants will be asked to wear the FitBit Charge 2 on the non-dominant arm and respond to the phone application daily for 4 weeks. Participants' peripheral blood will be drawn at week 1 and week 4 by a registered nurse or certified phlebotomist. We will ask the participant to have a sweat pad placed on their upper abdomen or flank for 72 hours to collect the sweat at baseline (before the program) and week 4 (at the program completion).

At the end of the program, a research team member will visit participants' home and evaluate the participants' perception and satisfaction for the program using a quantitative semi-structure interview. The interview will be recorded and transcribed for the qualitative analysis. Participants will be asked to complete the questionnaires. Participants' blood and sweat will be collected. The feasibility of the intervention program will be determined from the achievement of individual physical activity goal. At the end of 4 week program, research team will review the participants ability to achieve at least 75% of the individual's exercise goal (for example, if the goal is to exercise at the fat burn level (50-60% maximum heart rate measured by FitBit) for 30 min/day 3 days week, participants can exercise for 30 min for at least 2 days or FitBit data showed more than 60 active min). For this first phase, at least 50% of participants will need to meet 75% of personal goal in at least 2 weeks for the trial to continue onto phase II. For participants who do not achieve 75% of their individual exercise goal, the barriers will be identified that the weekly goals will be revised until the 75% of weekly personal exercise goals is met. If the feasibility threshold (less than 50% of participants achieve 75% of their weekly goals for 2 weeks) does not reach, we will adjust the goal setting process and recruit more participants. Moreover, we will descriptive information from the phase I to help inform alternative approaches to the anticipated analysis, sample size estimates for phase II, and additional key variables to be measured in phase II (intervention dose, fidelity, and .additional process variables).

Intervention

Tailored Technology-Enhance Home-based Exercise Program:

The tailored technology enhanced home-based exercise (iHBE) program is a 4-week program with 1 assessment home visit session, 4 home visits during exercise. The detail activities are presented in table 1. The technologies, a wearable device, and a smartphone application, will be used as a tool to monitor physical performance (heart rate, step count), provide immediate feedback, send daily reminding message through mEMA. The coded raw data without personal identification information from the wearable device will be sent to the servers where we can store it in the database alongside the mEMA data and create custom reports showing HR 30 minute before each EMA survey, showing HR and previous self-report responses before/ after each automatically triggered EMA.

Weeks	Program Activities
Assessment session (home visit; Week 0)	A research team member (research nurses and/or physical therapist) will meet and assess the participants' perception of PA and goals. Participants will complete the questionnaires for baseline symptoms, Affective Well Being (AWB) and resilience. Participants' blood and sweat will be collected. The research team will help the participants to identify the barriers, prioritize goals for weekly activity and make a plan to achieve these goals. Participants will be asked the perception of their ability to complete the six-minute walk and their exertion level, then choose the PA modality, frequency, duration and time of the day of their exercise based on their preference, and goals. Exercise intervention options Option 1: The NIA Go4Life exercise Option 2: Iyengar-style yoga 10-20 minutes on at least 2 days per week

Weeks	Program Activities
	Option 3: Walking to achieved the weekly goal (e.g., walk 5 min for 3 days/week and increase 1-2 min/week) Option 4: Modified Otago exercise intervention Participants will be trained to use the FitBit Charge 2 and mEMA application. During this home visit, participants will practice their selected exercise with a physical therapist or an RN, set the wearable device and record their HR, fatigue and pain level at the end of each exercise session on the mEMA. Participants will receive a booklet contains the information of their selected exercise intervention and a weekly planner.
4 home visits (Week 1-4)	A research team member will visit participants' home and evaluate exercise problems. The research team will review the physical performance with the participants and help them identify problems and solutions. During these visit, the research team will tailor the exercise to be suitable for the participants' conditions and situation. Participants will practice their exercise with the research team for 15-20 min. The information on home safety will be provided to the participants and their caregivers.
Completion session (end of week 4)	A research team member will visit participants' home and evaluate the participants' perception and satisfaction for the program using a quantitative semi-structure interview. Participants will be asked to complete the questionnaires. Participants' blood and sweat will be collected.

Table 1: iHBE program activities

Program fidelity: To maintain fidelity of the program, two research assistants/research nurse will receive 1-month project specific training on intervention design, all four exercise options and project implementation. Nurse researchers will receive additional training on how to demonstrate the use of technologies (a wearable device: FitBit Charge 2) and a smartphone application (mEMA) and how to conduct a physical function assessment set PA goals and identify problems and solutions. The nurse researchers will conduct a home visit and follow up phone call under the supervision of a registered nurse. The principal investigator will randomly check home visit and follow up phone call sessions and provide timely feedback. The investigator team will work with the nurse researchers and clinical settings for quality assurance and address any issues that may occur during the study.

Variables and measurements.

Physical function: To ensure participants' safety during home exercise and provide the best recommendation for the type of exercise, the physical function will be measured by asking the participants perception on their ability to complete a walk for 6 minutes with the perceived exertion level of 3 or below.

The study variables will be measured as follows:

Measure	Description	Psychometrics
NINR Common Data Elements (CDEs)	23-item; measure demographic and disease information data	
PROMIS Short Form V1.0-Fatigue 6a	6-items; self-reported fatigue (frequency, duration, intensity) and the impact on physical, mental, and social activities, has five response options (1 or never to 5 or always).	Initial psychometric properties have shown an internal consistency reliability coefficient of greater than 0.80.[52]

Measure	Description	Psychometrics
PROMIS Pain Intensity – Short Form 3a V1.0.	Universal and not a disease-specific instrument for pain, 3-items (worst, average, and current pain) measure from 1 (no pain) to 5 (very severe).	Conceptually validated with established reliability Test-retest values = .83 to .93.(PROMIS, 2015)
Wrist-worn wearable device: Microsoft band 2	PA (steps count and Heart rate) tracking device (wrist-worn)	Intraclass Correlation Coefficients with ActivPAL are 0.81 and 0.96 respectively, $p < .01$.(Kooiman et al., 2015)
Connor-Davidson Resilience Scale	10 item self-report rating scale 0 (not true at all) to 4 (true nearly all the time)	Good internal consistency (Cronbach's alpha 0.85) and constructs validity.(Campbell-Sills & Stein, 2007)
Short form survey (SF-36)	36 item self-report instrument measure 2 domains: physical well-being and affective well-being.	Good internal consistency for every scales (Cronbach's alpha ≥ 0.70).(Busija et al., 2011)

Serum and Sweat BDNF protein levels will be measured by the enzyme-linked immunosorbent assay (ELISA). Participants' peripheral blood will be drawn during home visits, the sweat patch will be placed on the participants' upper abdomen or flank for 72 hours to collect the sweat at baseline and the program completion (week 4). The ELISA will be performed according to the manufacturer's guide by one laboratory technician.

Data Collection Schedule and Procedures:

Phase one: intervention trial phase (open-label phase). Upon receiving approval from the Johns Hopkins Institutional Review Board and the participant's informed consent is signed. Eight participants who have completed treatment for a solid tumor cancer with at least one comorbidity (e.g., diabetes and/or hypertension) will be assigned to an open-label trial of the iBHE (see table 1 for detail activities).

We will explore measurement of variables, exercise choices and tracking mechanisms with participants regarding feasibility and acceptability. The principal investigator will conduct a qualitative semi-structured interview, record and take notes of the interview and discussed participants' feedback with the research teams. The exercise plan, wearable device, and phone application feature will be discussed until consensus program for each option is made.

Table : Data collection process

Task	home visit Baseline: Assessment Week 0	iBHE program				Post intervention
		Home visits week				Home visit
		1	2	3	4	
Assessment: perception, goal, FTSST, and 6MWT	X					
Demographic and disease information questionnaire	X					
PROMIS fatigue and PROMIS pain	X					X
Short form survey (SF-36)	X					X
Connor-Davidson Resilience Scale	X					X
Physical activity (steps) and HR (from wearable device)*	X	X	X	X	X	X
Blood sample for BDNF level	X					X
Sweat sample for BDNF level	X					X

*objective physical activity will be measured daily

5. Inclusion/Exclusion Criteria

Inclusion criteria are (1) participants diagnosed with solid tumor cancer who have completed cancer treatment at least 6 months; (2) diagnosed with diabetes and/or hypertension for at least a year; (3) aged 21 years or older, (4) have an annual household incomes of below $30,000 for families of three, (5) the average fatigue level within the past 7 days at the level of 3 or more on the 0 (no fatigue) to 10 (worse fatigue) Likert scale and (6) give informed consent.

Exclusion criteria are those (1) currently undergoing treatment for cancer; (2) have an active infection (e.g., fever, localized redness, swelling, sinus congestion); and/or (3) diagnosed with a psychological disorder (e.g., suicidal or homicidal tendencies, extreme anxiety or depression).

6. Drugs/ Substances/ Devices

None

7. Study Statistics

Data analysis:

Phase 1:

Aim 1: Examine the feasibility and acceptability of the iBHE program among low-income cancer survivors living with co-morbid conditions.

Primary objectives of this phase are to evaluate the feasibility and acceptability of the iBHE program. Eight participants who have completed treatment for a solid tumor cancer with at least one comorbidity (e.g., diabetes and/or hypertension) will be assigned to an open-label trial of the iBHE. At the completion of the program (4 weeks), the primary investigator will conduct a semi-structured interview to gather feedback on the program feasibility, goal setting, problem-solving strategies, exercise choices and tracking mechanisms, program feasibility, and acceptability. The interview will be recorded and transcribed verbatim.

The feasibility of the program

The feasibility of the intervention program will be determined from the achievement of individual physical activity goal. At the end of 4 week program, research team will review the participants ability to achieve at least 75% of the individual's exercise goal (for example, if the goal is to exercise at the fat burn level (50-60% maximum heart rate measured by FitBit) for 30 min/day 3 days week, participants can exercise for 30 min for at least 2 days or FitBit data showed more than 60 active min). For this first phase, at least 50% of participants will need to meet 75% of personal goal in at least 2 weeks for the trial to continue onto phase II. For participants who do not achieve 75% of their individual exercise goal, the barriers will be identified that the weekly goals will be revised until the 75% of weekly personal exercise goals is met. If the feasibility threshold (less than 50% of participants achieve 75% of their weekly goals for 2 weeks) does not reach, we will adjust the goal setting process and recruit more participants.

The feasibility of the recruitment will be determined by the number of screened participants, eligible participants and participants who refuse to be in the study and rational will be examined and recorded as indicator of feasibility. The feasibility of delivering the program will be evaluated by examining the number and timing for actual versus planned home visit and the duration of each visit. The intervention checklist will be filled by the research assistants for each home visit to assess the intervention content delivery.

The acceptability of the program

The acceptability of the program will be assessed using the semi-structure interview. The common feedback and suggestion for intervention during the semi-structure interview will be noted.

The compliance of the program

The compliance of this program will be monitored using active min and daily heart rate zone data from the wearable device (FitBit Charge 2). The weekly goals on number of day for physical activity and duration of the physical activity will be set. The number active min and duration of the heart rate in at least "Fat Burn" zone per day will be recorded for the duration of physical activity/day. The number of days the participant achieve the goals (duration and days) for physical activity will be used to measure the compliance of the program.

The descriptive information from the phase I to help inform alternative approaches to the anticipated analysis, sample size estimates for phase II, and additional key variables to be measured in phase II (intervention dose, fidelity, and .additional process variables).

The program modification

Prior to phase 2, the primary investigator will discuss participants' feedback with the research teams. The modification of exercise plan, wearable device, and phone application feature will be discussed until consensus program for each option is made.

8. Risks

Potential Risks:

The risks of participating in this study are minimal. Potential risks include

1. complications during the blood drawing for examples pain and bleeding at the drawing site.
2. complications during the sweat collection for examples rash, itching, redness and swollen.
3. minimum discomfort might occur during the wearable device (worn like a bracelet).
4. complications (e.g., fainting, injury) during the exercise program.

During the proposed study, if there is a serious adverse event, anticipated to be an uncommon occurrence, the PI will unmask treatment group assignment when necessary for the safety of the participant. The administration of the intervention may be discontinued at the participant's request or by the investigator, based on clinical judgment. Participants will be instructed to report any adverse event experienced after treatment without delay.

Adequacy of Protection against Risks: The safety of the study participants is essential. The primary investigator and research team will take all precautions to protect the participants against risks.

Protection against Risks: The principal investigator (PI) and research team plan to prevent the following risks:

1. Complications of the blood drawn. Participants may experience pain and discomfort during the blood drawn. They may also be at risk of bleeding. All of the blood drawn will be performed by register nurses. After blood drawn, participants' conditions will be monitored by a registered nurse.
2. Complications of the sweat collection. Participants may experience allergic reactions and discomfort during the sweat collection. The sweat pad will be placed by the train research team members. Participants will be informed of the sign and symptoms of a potential allergic reaction. The pad can be easily removed if participants experience discomfort.
3. Minimum discomfort might occur while wearing the wearable device (worn like a bracelet). Participants will be asked to wear a physical tracking wearable device to measure their activity and sleep duration. This equipment may cause the discomfort. As with any type of jewelry, some people may experience allergies. Some people may experience a rash wearing the device. The device can be easily removed if discomfort is experienced.
4. Complications (e.g., fainting, injury, fall) during the exercise program. All four exercise option is low intensity, low impact exercise program, which will be conducted by the trained research nurse or physical therapist. During the first four weekly home visit, research nurse

and/or physical therapist will monitor the participants exercise to ensure appropriate body alignment and posture and participants safely. All participants will be asked to wear appropriate shoes and comfortable cloth during the exercise.

9. Benefits

There is no direct benefit to the participant from being in this study. However, the home-based, tailored, technology-enhanced exercise program (iHBE) proposed in this study could be used as alternative choices for cancer survivors to manage their fatigue and improve patients' quality of life. The mEMA application and wearable device can serve as useful tools for health care providers to monitor intervention outcomes and compliance while the patients are at home.

10. Payment and Remuneration

Phase 1 (Aim 1) - Participants will receive $40 for their time in completing the baseline data and the interview

11. Costs

There will be no cost for participants to participate in this study.

12. Data Safety Monitoring Plan

The PI will review reports reflecting data quality, safety, and monitor for potential adverse events and protocol adherence. The project coordinator, study staffs will meet with the PI weekly to review the progress of the study. The members of the investigative team and scientific advisors will meet monthly to support the study. A Safety Monitoring Committee (SMC) will be formed, consisting of Johns Hopkins University clinician faculty members who are independent of this proposed feasibility study. The SMC will be responsible for overall monitoring of the safety of participants in this proposed study and overseeing the PI, Co-Is, and research assistant.

The PI will be responsible for managing all data, securing privacy and confidentiality, minimizing and identifying risks, monitoring and reporting adverse events or any safety issues, and complying with timely reporting requirements to all applicable regulatory bodies for any adverse events or unexpected problems. Monthly reports will be completed by the PI detailing participant demographics, recruitment status, treatment retention rates, protocol compliance, data gathered and accuracy, and quality assurance or regulatory issues that transpired, and summary of any adverse events. The research team (PI, Co-Is, and research assistant) will meet weekly via face to face or conference calling to discuss data and safety monitoring.

The SMC will meet annually (or more frequently if needed) and review the annual reports completed by the PI; review study safety, integrity, and progress including any adverse events; provide advice in relation to continuing, changing, or terminating the study when necessary; require more frequent reporting as needed; audit the study for compliance and verify authenticity of data; and assess that the research team is complying with informed consenting and other required regulations. These annual meetings will be conducted face-to-face or through conference calls.

The PI, in consultation with the SMC, will provide reports at intervals as required by National Institute of Health and/or other regulatory bodies as well as provide immediate reports as required regarding any adverse or unanticipated problems that may occur.

Phase 2*: *Pilot testing the adjusted iHBE program

4. Study Procedures

Design: Randomized waiting list controlled trial design

Phase 2 Specific Aims

Aim 2: Pilot testing the effect of the tailored iHBE on fatigue, pain, affective well-being, resilience and BDNF level among low-income cancer survivors living with co-morbid conditions at completion (12 weeks) and 6 months in comparison to usual care waiting list group.
After adjustment in the protocol based on Aim 1, 50 participants who meet the inclusion criteria will be randomly assigned to a 12-week experimental (preferred physical activities) group or a usual care usual care (waiting list) group. Variables will be measured at baseline, completion (12 weeks) and 6 months. *Hypothesis 2: After controlling for the age, gender, race, and BMI, participants in the experimental group will have a greater decline in fatigue, pain, and a greater increase in AWB, resilience and BDNF level from baseline to program completion and 3 months compared to the usual care group.*

Aim 3: Examine the association between the changes in the biomarker (BDNF) in serum and sweat after the 12-weeks from baseline and at 3 months post program completion from baseline iBHE program. *Hypothesis 3: the change in the serum BDNF level is positively associated with a change in the sweat BDNF level at the after the 12-weeks from baseline and at 6 months from baseline iBHE program.*

Sample and Setting:

The study participants will be recruited from the home health care agencies in Baltimore, Maryland, Johns Hopkins Comprehensive Cancer Center and Johns Hopkins Hospital.

Inclusion criteria are (1) participants diagnosed with solid tumor cancer who have completed cancer treatment at least 6 months; (2) diagnosed with diabetes and/or hypertension for at least a year; (3) aged 21 years or older, (4) have an annual household incomes of below $30,000 for families of three, (5) the average fatigue level within the past 7 days at the level of 3 or more on the 0 (no fatigue) to 10 (worse fatigue) Likert scale and (6) give informed consent.

Exclusion criteria are those (1) currently undergoing treatment for cancer; (2) have an active infection (e.g., fever, localized redness, swelling, sinus congestion); and/or (3) diagnosed with a psychological disorder (e.g., suicidal or homicidal tendencies, extreme anxiety or depression).

Sample size justification

Phase 2: With an alpha level of .05, the statistical power of 0.80, and 25 participants per group, we will be able to detect significant differences of moderate to large effect sizes of 0.65 when comparing change across baseline, 3-months, and 6-months between the two groups. With an attrition rate of 12% (22 participants per group), the detectable effect size increases to 0.69. Since this is a pilot study and not powered to detect small to moderate effect sizes, we will pay close attention to the effect size, rather than statistical significance. These effect size estimates will be used to inform future research trials.

Randomization: Eligible participants will be randomized in a 1:1 allocation ratio to one of the two treatment arms. The electronic Research Electronic Data Capture (REDCap), a randomization application will be used to randomly assigned the participants to the groups

Data Collection Schedule and Procedures. Upon receiving approval from the Johns Hopkins University Institutional Review Board, the study flyer will be posted and distributed at the home health care agencies in Baltimore, Maryland, Johns Hopkins Comprehensive Cancer Center and Johns Hopkins Hospital.

Recruitment, Informed Consent, and Confidentiality. Recruitment methods for this study include (1) distributing and posting flyers, with a tear-off phone number to speak with the principal investigator (PI) as necessary, posted at the hospital (2) face-to-face recruitment for potential participants during cancer support group meetings; and (3) word-of-mouth. Potential participants will receive a verbal explanation by phone or face to face meeting in terms suited to their comprehension of the purpose, procedures, and potential risks of the study. During the screening for eligibility process, an oncologist will be available for consultation. The oncologist will be notified and consulted for the appropriateness of the exercise for participants who self-report having co-morbidities. The participants and family or legal guardian will have an opportunity to carefully review the consent form and ask questions regarding this study prior to signing. Participants will be encouraged to consult with their primary doctor if any concern or an additional question. Participants will be informed that they may withdraw from the study at any time without prejudice to themselves.

Participants will be approached and screened for the annual income below $30,000 for families of three, average fatigue level within the past 7 days at the level of 3 or more on the 0 (no fatigue) to 10 (worse fatigue) Likert scale, the self-report perceived ability to walk for six-minute and the exertion level after the walk on a 0-10 numeric perceived exertion scale (0 = no exertion at all to 10 = maximal exertion). Eligible participants will be asked if they would like to participate and to sign the informed consent. Participants will be asked to have the research team visit their home for the initial assessment and to provide instruction on the exercise, the physical activity tracker and how to complete the questionnaire via the phone application for 4 weeks, followed by phone follow up for 7 weeks. Participants will be asked to wear the FitBit Charge 2on the non-dominant arm and respond to the phone application daily for 12 weeks. Participants' peripheral blood will be drawn at week 1 and week 12 by a registered nurse or certified phlebotomist. We will ask the participant to have a sweat pad placed on their upper abdomen or flank for 72 hours to collect the sweat at baseline (before the program) and week 12 (at the program completion).

At the end of the program, a research team member will visit participants' home and evaluate the participants' perception and satisfaction for the program using a open ended questionnaires. Participants will be asked to complete the questionnaires. Participants' blood and sweat will be collected.

Intervention/Independent Variables

Tailored Technology-Enhance Home-based Exercise Program:

The tailored technology enhanced home-based exercise (iHBE) program: Participants in this group will receive an adjusted (based on the feedback from phase 1)12-week program with 1 assessment home visit session, 5 home visits during exercise and 7 follow up phone calls. The technologies, a wearable device and a smartphone application, will be used as a tool to monitor physical performance (heart rate, step count), provide immediate feedback, send daily reminding message through mEMA. The coded raw data without personal identification information from the wearable device will be sent to the servers where we can store it in the database alongside the mEMA data and create custom reports showing HR 30 minute before each EMA survey, showing HR and previous self-report responses before/ after each automatically triggered

EMA.

Usual Care (Waiting List) Group: The usual care waiting list group will receive educational booklets about a healthy lifestyle and cancer survivorship. Participants will be asked to wear the wearable device during the waiting period to monitor the PA (steps and heart rate).They will receive a notification to rate their daily fatigue level for 3 months. Usual Care participants will receive the iHBE after the conclusion of the study (as described above).

Variables and measurements.

The study variables will be measured as follows:

Measure	Description	Psychometrics
NINR Common Data Elements (CDEs)	23-item; measure demographic and disease information data	
PROMIS Short Form V1.0-Fatigue 6a	6-items; self-reported fatigue (frequency, duration, intensity) and the impact to physical, mental, and social activities, has five response options (1 or never to 5 or always).	Initial psychometric properties have shown an internal consistency reliability coefficient of greater than 0.80.[52]
PROMIS Pain Intensity – Short Form 3a V1.0.	Universal and not disease-specific instrument for pain, 3-items (worst, average, and current pain) measure from 1 (no pain) to 5 (very severe).	Conceptually validated with established reliability Test-retest values = .83 to .93.(PROMIS, 2015)
Wrist worn wearable device: FitBit Charge 2	PA (steps count and Heart rate) tracking device (wrist worn)	Intraclass Correlation Coefficients with ActivPAL are 0.81 and 0.96 respectively, $p < .01$.(Kooiman et al., 2015)
Connor-Davidson Resilience Scale	10 item self-report rating scale 0 (not true at all) to 4 (true nearly all the time)	Good internal consistency (Cronbach's alpha 0.85) and constructs validity.(Campbell-Sills & Stein, 2007)
Short form survey (SF-36)	36 item self-report instrument measure 2 domains: physical well-being and affective well-being.	Good internal consistency for every scales (Cronbach's alpha ≥ 0.70).(Busija et al., 2011)

Serum and Sweat BDNF protein levels will be measured by the enzyme-linked immunosorbent assay (ELISA). Participants' peripheral blood will be drawn during home visits, the sweat patch will be placed on the participants' upper abdomen or flank for 72 hours to collect the sweat at baseline, 12 weeks and 3 months after the program completion. The ELISA will be performed according to manufacturer's guide by one laboratory technician.

Data Collection Schedule and Procedures:

Phase two is a pilot testing of the adjusted iHBE program effectiveness on the symptoms (fatigue and pain) affective well-being, resilience and BDNF level. A randomized usual care (waiting list) trial phase will be used. The study flyers will be posted at the home health care agencies, Johns Hopkins Comprehensive Cancer Center and Johns Hopkins Hospital. Eligible participants will be contacted by the principal investigator or research assistant who will explain the purpose of the study and requirements, and provided the study information and consent form. After providing the signed consent form, participants will complete the baseline assessment including the questionnaire, physical function (FTSST and 6MWT)

and blood samples. A pre-installed application smartphone and a wrist-worn wearable device (FitBit Charge 2) will be loaned to the participants. The online account specific to the participant will be assigned using code. No personal information will be stored separately. Participants will be asked to wear the FitBit Charge 2 on the non-dominant arm and respond to the mEMA application to monitor their free-living PA level for 7 days then randomly assigned to the experiment and usual care waiting list group. Participants in the iHBE group will receive one assessment home visit, 5 home visits and 7 follow up phone calls during the iHBE program. Then a home follows up visit at 6 month. The usual care (waiting list) group will receive educational booklets about a healthy lifestyle. They will be asked to continue to wear the wearable device to monitor PA for 3 months. Participants will then receive the iHBE program after the conclusion of the 12-week program.

5. Inclusion/Exclusion Criteria

Inclusion criteria are (1) participants diagnosed with solid tumor cancer who have completed cancer treatment at least 6 months; (2) diagnosed with diabetes and/or hypertension for at least a year; (3) aged 21 years or older, (4) have an annual household incomes of below $30,000 for families of three, (5) the average fatigue level within the past 7 days at the level of 3 or more on the 0 (no fatigue) to 10 (worse fatigue) Likert scale and (6) give informed consent.

Exclusion criteria are those (1) currently undergoing treatment for cancer; (2) have an active infection (e.g., fever, localized redness, swelling, sinus congestion); and/or (3) diagnosed with a psychological disorder (e.g., suicidal or homicidal tendencies, extreme anxiety or depression).

6. Drugs/Substances/Devices

None

7. Study Statistics

Phase 2 Data analysis

To test ***Hypothesis 2*** *(Aim 2)* examining the effectiveness of iHBE program on fatigue, pain, well-being, resilience and BDNF levels, generalized estimating equations (GEE) will be used. The models will include time as a within-subject fixed effect (baseline, 3 months, 6 months), group (intervention vs usual care) as a fixed-effect between-subject factor and the group by time interaction. Baseline age, race gender, and BMI will be included as covariates. A significant group by time interaction would signify that the change over time in the outcomes differed for the intervention and usual care groups. GEE was selected because it uses all available data and does not require complete data across time for a participant to be included in the analyses. Correlation will be used to test the relationship between the changes in serum and sweat BDNF levels ***(Aim 3).*** Change from baseline to 3 months and change from baseline to 6 months will be computed for serum BDNF and separately for sweat BDNF. The correlation between the change scores measured by the different modes will be estimated at each time point

8. Risks: Same as phase 1

9. Benefits: Same as phase 1

10. Payment and Remuneration

Phase 2 (Aim 2 and 3) - The participants in both the intervention group and the control group will each receive a total of $80 ($20 at the start of the intervention, $30 the end of the intervention and $30 at 6 months)

11. Costs

There will be no cost for participants to participate in this study.

12. Data Safety Monitoring Plan

The PI will review reports reflecting data quality, safety, and monitor for potential adverse events and protocol adherence. The project coordinator, study staffs will meet with the PI weekly to review the progress of the study. The members of the investigative team and scientific advisors will meet monthly to support the study. A Safety Monitoring Committee (SMC) will be formed, consisting of Johns Hopkins University clinician faculty members who are independent of this proposed feasibility study. The SMC will be responsible for overall monitoring of the safety of participants in this proposed study and overseeing the PI, Co-Is, and research assistant.

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